perfusate. The method requires the steps of providing a microdialysis probe, a measurement cell, and a control device, inserting the microdialysis probe into the body fluid, passing the perfusate having a starting content of glucose through the microdialysis probe in alternating successive transport and dialysis intervals at different flow rates to obtain a dialysate, transporting the dialysate to the measuring cell, measuring measurement signals that correlate with the glucose content of the dialysate, adjusting the starting content of glucose in the perfusate to the glucose content of the body fluid with the control device in accordance with a command variable corresponding with the glucose concentration of the body fluid and being derived from the measurement signals of the measuring cell, and using a momentary starting content of glucose in the perfusate as a measure for the glucose content of the body fluid or determining the glucose content of the body fluid directly from obtained measurement signals. Support for the new claim is found throughout the specification and drawings. No new matter is added by virtue of the new claim. Claims 69-79 depend from claim 68.

Claims 23-50 are rejected under 35 U.S.C. 112, second paragraph as being indefinite. Claim 23 has been amended to require that the step of "using a momentary starting content of glucose in the perfusate as a measure for the glucose content of the body fluid or determining the glucose content of the body fluid directly from obtained measurement signals". Claim 23 has also been amended to recite that the method of the present invention is directed to a method for "continuously determining the glucose concentration in a body fluid with glucose-containing perfusate". Finally, claim 23 has been amended to recite that a command variable corresponds with "the glucose concentration of the body fluid derived from the measurement signals of the measuring cell". Support for the amendments is found in the specification and particularly at page 4 lines 5-9, page 8 lines 10-13, and page 10 lines 12-18. No new matter is believed to be added by virtue of the amendments.

Claims 25 and 26 have each been amended to correct a typographical error and to require that "the adjusting step includes initially determining the starting content of glucose in the perfusate by comparing the adjusting variable with corresponding normalized values of the glucose concentration in the body fluid". Support for the amendments is found in the specification at page 3 lines 9-17 and page 11 lines 11-24, and page 12 lines 4-17. No new matter is believed to be added by virtue of the amendments. Claims 23 and 25-26 as amended are believed to be

sufficiently definite for purposes of 35 U.S.C. 112, second paragraph. Claims 24-50 depend from amended claim 23. Accordingly, reconsideration of the rejection leading to its withdraw and allowance of the claims is respectfully requested.

Reconsideration of the rejection of claims 23-50 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,091,976 to Pfeiffer et al. in light of the following remarks is respectfully requested.

Pfeiffer et al. relates to a method for determining and monitoring tissue glucose concentration. In a preferred implementation of the invention, the perfusion solution is mixed with glucose before being made to pass through the microdialysis probe and a predetermined initial concentration is set, preferably within the physiological range. See Col. 1 lines 59-63.

In order to support an obviousness rejection, it is necessary that Pfeiffer et al. provide some teaching, suggestion, or incentive to be modified as proffered by the rejection. Here, it is submitted that Pfeiffer et al. fails to teach or suggest the step of "adjusting the starting content of glucose in the perfusate . . . in accordance with a command variable corresponding with the glucose concentration of the body fluid and being derived from the measurement signals of the measuring cell".

It is submitted that Pfeiffer et al. at most teaches setting an initial glucose concentration in the perfusion solution, which is maintained unchanged during testing. The Examiner's attention is directed, to Col. 1 line 59-62, where it is taught, "the perfusion solution is mixed with glucose . . . and a predetermined initial concentration is set". Further, at Col. 2 lines 1-6, Pfeiffer et al. teaches that, "subsequent perfusion solution . . . essentially retains its initial glucose concentration. Accordingly a base line reflecting the initial glucose concentration is picked up during the subsequent flow".

Thus, at most, Pfeiffer et al. teaches monitoring tissue glucose using a set predetermined glucose base line. This teaching runs contrary to that of the method of amended claim 23, which requires "adjusting the starting content of glucose in the perfusate . . . in accordance with a command variable corresponding with the glucose concentration of the body fluid and being derived from the measurement signals of the measuring cell".

Accordingly, it is submitted that only with hindsight, in view of Applicants specification, could one of skill in the art derive from Pfeiffer et al. a suggestion to the invention as it is presently claimed. It is therefore respectfully submitted that Pfeiffer

et al. cannot be said to provide suggestion or motivation to be modified to meet the requirements of amended claim 23, that being a method for continuously determining the glucose concentration in a body fluid with glucose-containing perfusate, wherein the method comprises the steps of "passing the perfusate having a starting content of glucose through the microdialysis probe to obtain a dialysate, transporting the dialysate to the measuring cell, measuring measurement signals that correlate with the glucose content of the dialysate, adjusting the starting content of glucose in the perfusate to the glucose content of the body fluid with the control device in accordance with a command variable corresponding with the glucose concentration of the body fluid and being derived from the measurement signals of the measuring cell, and using a momentary starting content of glucose in the perfusate as a measure for the glucose content of the body fluid or determining the glucose content of the body fluid directly from obtained measurement signals". Claims 24-50 depend from amended claim 23.

It is respectfully contended that the differences between the claimed invention and the cited art are such that Applicants' invention as a whole would not have been obvious to one of ordinary skill in the art at the time the invention was made. It is respectfully contended that the claimed invention meets the test of patentability under 35 U.S.C. 103(a). Entry of the amendments leading to reconsideration of the rejection of the claims and withdrawal of the rejection is respectfully requested.

This application is deemed to be in condition for allowance and as such is respectfully requested. In addition, it is requested that if necessary, that this paper be considered as a Petition for an Extension of Time sufficient to effect a timely response and fees be charged to Deposit Account No. 50-0877.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

23. (Amended) A method for continuously determining the glucose concentration in a body fluid with glucose-containing perfusate, the method comprising the steps of:

providing a microdialysis probe, a measurement cell, and a control device,

inserting the microdialysis probe into the body fluid,

passing the perfusate having a starting content of glucose through the microdialysis probe to obtain a dialysate,

transporting the dialysate to the measuring cell,

measuring measurement signals that correlate with the glucose content of the dialysate, [and]

adjusting the starting content of glucose in the perfusate to the glucose content of the body fluid with the control device in accordance with a command variable corresponding with the glucose concentration of the body fluid and being derived from the measurement signals of the measuring cell, and

using a momentary starting content of glucose in the perfusate as a measure for the glucose content of the body fluid or determining the glucose content of the body fluid directly from obtained measurement signals.

25. (Amended) The method of claim 24 wherein the control [unit] device includes an adjuster having an adjusting variable and the adjusting step includes initially determining the starting content of glucose in the perfusate [from] by comparing the adjusting variable with corresponding normalized values of the glucose concentration in the body fluid.

26. (Amended) The method of claim 23 wherein the control [unit] device includes an adjuster having an adjusting variable and the adjusting step includes initially determining the starting content of glucose in the perfusate [from] by comparing the adjusting variable with corresponding normalized values of the glucose concentration in the body fluid.

[51. An arrangement for determining the glucose concentration in a body fluid, the arrangement comprising

a microdialysis probe formed for a diffusion exchange of glucose with surrounding body fluid,

a perfusion device formed to perfuse the microdialysis probe with glucose-containing perfusate to obtain a dialysate,

a measuring cell located after the microdialysis probe, the cell being formed to detect measurement signals that correlate with the glucose content of the dialysate, and

a control device that adjusts the starting content of glucose in the perfusate to the glucose content of the body fluid in accordance with a command variable derived from the measurement signals of the measuring cell.]

[52. The arrangement of claim 51 further comprising an evaluation unit formed to determine the momentary starting content of glucose in the perfusate when the control deviation is negligible as a measure for the glucose content of the body fluid.]

[53. The arrangement as claimed in claim 52 wherein the perfusion device has a perfusate store and a transport unit that is formed for the intermittent transport of perfusate.]

[54. The arrangement as claimed in claim 51 wherein the perfusion device has a perfusate store and a transport unit that is formed for the intermittent transport of perfusate.]

[55. The arrangement as claimed in claim 54 wherein the perfusate store has at least two separate reservoirs to hold perfusion liquids with different glucose concentrations.]

[56. The arrangement as claimed in claim 54 wherein the perfusate store has a first reservoir containing a glucose-free perfusion liquid and a second reservoir containing a glucose-containing perfusion liquid.]

[57. The arrangement as claimed in claim 54 wherein the control device has a flow mixer that includes a valve formed to adjust the starting content of the glucose in the perfusate.]

[58. The arrangement as claimed in claim 51 wherein the control device has a flow mixer that includes a valve formed to adjust the starting content of the glucose in the perfusate.]

[59. The arrangement as claimed in claim 58 wherein the valve is mixing valve or a clock-pulsed directional control valve.]

[60. The arrangement as claimed in claim 52 wherein the control device has a flow mixer that includes a valve formed to adjust the starting content of the glucose in the perfusate.]

[61. The arrangement as claimed in claim 58 wherein the flow mixer includes an inlet side connected to reservoirs for feeding in perfusion fluids with different glucose contents and an outlet side connected to a perfusate tube leading to the microdialysis probe.]

[62. The arrangement as claimed in claim 58 wherein the control device has a digitally operated controller.]

[63. The arrangement as claimed in claim 51 wherein the control device has a digitally operated controller.]

[64. The arrangement as claimed in claim 63 wherein the controller is a microcontroller.]

[65. The arrangement as claimed in claim 52 wherein the control device has a digitally operated controller.]

[66. The arrangement as claimed in claim 54 wherein the control device has a digitally operated controller.]

[67. An system for determining the glucose concentration in a tissue fluid, the system comprising:

a microdialysis probe formed to be inserted into the tissue fluid,

reservoirs formed to hold perfusion liquids with different glucose contents,

a transport unit formed to perfuse the microdialysis probe with glucose-containing perfusate to obtain dialysate,

a flow-through measuring cell downstream of the microdialysis probe, the cell being formed to register measurement signals that correlate with the glucose content of the dialysate, and

a control device connected to the measuring cell, the control device including a flow mixer having an inlet side connected to the reservoirs and an the outlet side connected to the microdialysis probe, the flow mixer being formed to act as an adjuster to regulate the starting content of glucose in the perfusate.]

68. A method for continuously determining the glucose concentration in a body fluid with glucose-containing perfusate, the method comprising the steps of:

providing a microdialysis probe, a measurement cell, and a control device,

inserting the microdialysis probe into the body fluid,

passing the perfusate having a starting content of glucose through the microdialysis probe in alternating successive transport and dialysis intervals at different flow rates to obtain a dialysate,

transporting the dialysate to the measuring cell,

measuring measurement signals that correlate with the glucose content of the dialysate,

adjusting the starting content of glucose in the perfusate to the glucose content of the body fluid with the control device in accordance with a command variable corresponding with the glucose concentration of the body fluid and being derived from the measurement signals of the measuring cell, and

using a momentary starting content of glucose in the perfusate as a measure for the glucose content of the body fluid or determining the glucose content of the body fluid directly from obtained measurement signals.

69. The method of claim 68 wherein the adjusting step includes determining a momentary starting content of the glucose in the perfusate as a measure for the glucose content of the body fluid when a deviation of a controlled variable from the command variable is negligible.

70. The method of claim 69 wherein the control unit includes an adjuster having an adjusting variable and the adjusting step includes initially determining the starting content of glucose in the perfusate by comparing the adjusting variable with corresponding normalized values of the glucose concentration in the body fluid.

71. The method of claim 68 further comprising the step of measuring the glucose content of the perfusate before it is passed into the microdialysis probe.

72. The method of claim 68 further comprising the step of flow mixing two perfusion liquids with different glucose concentrations provided in two separate reservoirs to influence the starting content of glucose in the perfusate.

73. The method of claim 68 wherein the flow rate during the transport intervals is increased to such an extent that the starting content of glucose in the perfusate during passage through the microdialysis probe remains essentially constant and that during the dialysis intervals the transport is interrupted or at least the flow rate is reduced to such an extent that the glucose concentration of the dialysate approximates the glucose content of the body fluid.

74. The method of claim 73 wherein the command variable is determined from the peak value of the signal time course of the measurement signals during each transport interval.

75. The method of claim 68 wherein the command variable is determined from the peak value of the signal time course of the measurement signals during each transport interval.

76. The method of claim 68 wherein the command variable is determined according to the glucose content c of the body fluid according to the relationship

$$c = \left[\frac{S_g}{S_g \cdot (1-b) + b \cdot S_0} - 1 \right] \cdot a \cdot c_0 + c_0$$

in which S_g denotes the peak value and S_0 denotes the base line value of the signals measured during a transport interval and c_0 is the momentary starting content of glucose in the perfusate and a, b are empirically determined correction factors compensating for diffusion and mixing and remaining recovery effects during the transport interval.

77. The method of claim 68 wherein the command variable is determined by integration or differentiation of the time course of the measurement signals.

78. The method of claim 68 wherein the command variable is determined by comparing the actual signal curve of the measurement signals with calibrated signal patterns deposited in a storage medium.

79. The method of claim 68 further comprising the step of regulating discontinuously the starting content of glucose in the perfusate by a two-point control process in which the starting content of glucose in the perfusate is changed by a predetermined adjustment value when there is a control deviation.